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Lactated Ringer's Solution Alleviates Brain Trauma-Precipitated Lactic Acidosis in Hemorrhagic Shock

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ABSTRACT

To determine the influence of brain trauma on blood acid-base and lactate-pyruvate responses to hemorrhage, and the effect of lactated Ringer's solution on these responses, 30 anesthetized rats were assigned to four groups: hemorrhage (n = 7), hemorrhage following fluid percussion brain trauma (trauma-hemorrhage group) (n = 7), hemorrhage treated with lactated Ringer's solution (hemorrhage-resuscitation group) (n = 8), and hemorrhage following brain trauma treated with lactated Ringer's solution (trauma-hemorrhage–resuscitation group) (n = 8). The hemorrhage group showed no significant changes in pH, HCO_3, and base excess after hemorrhage. Base excess and pH were significantly reduced after the hemorrhage in the trauma-hemorrhage group but were raised after resuscitation in the hemorrhage-resuscitation group. Acid-base values showed no difference between the trauma-hemorrhage–resuscitation and hemorrhage groups. The trauma-hemorrhage–resuscitation group also had a significantly higher base excess than the trauma-hemorrhage group. Lactate rose significantly after hemorrhage in the hemorrhage group and was even higher in the trauma-hemorrhage group, but there were no differences between the hemorrhage versus hemorrhage-resuscitation or trauma-hemorrhage–resuscitation groups. Both brain trauma and lactated Ringer's solution increased pyruvate with marked reduction in the ratio of lactate to pyruvate. These data indicate that brain trauma precipitates blood lactate accumulation and metabolic acidosis after hemorrhage, and infusion of lactated Ringer's solution can relieve these disturbances.

INTRODUCTION

Hemorrhage and resultant tissue hypoperfusion have been shown to increase the arterial lactate level and induce a metabolic acidosis (Perret and Enrico, 1978; Hardaway, 1981). Clinical and experimental studies indicate that a high lactate level is correlated with a poor prognosis in hemorrhagic shock (Hardaway,

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1981; Wade et al., 1989). Hemorrhagic shock is often accompanied by injuries in the central nervous system (Miller and Becker, 1982). However, little is known about the effect of brain trauma on the blood lactate response to hemorrhage. Furthermore, there are fewer studies addressing the question of treatment of combined hemorrhagic shock and brain trauma than studies addressing the treatment of hemorrhagic shock alone. An intravenous infusion of lactated Ringer's solution, the standard regime and the first choice of treating acute hemorrhage (Altmann and Dittmer, 1974), has not been validated for use in hemorrhagic shock combined with brain trauma. The efficacy of lactated Ringer's solution in correction of metabolic derangement in this combined clinical setting is unknown.

The present study was designed to determine if brain trauma alters acid-base and lactate-pyruvate responses to hemorrhage and to determine the extent to which an infusion of lactated Ringer's solution can affect these responses in a combined hemorrhagic shock-brain trauma setting.

MATERIALS AND METHODS

Experimental Protocol

Thirty male Sprague-Dawley rats (weight range, 325–482 g) were used in the present study. Anesthesia was iduced in a halothane chamber for 1 or 2 minutes and maintained initially by an intramuscular injection (1.3 ml/kg) of an equal volume mixture of ketamine hydrochloride (50 mg/ml) and xylazine (10.0 mg/ml). This was supplemented intramuscularly by 0.65 ml/kg 1 hour later. After another hour, a continuous intravenous infusion of the mixture was started at 0.2 ml/kg/h and maintained throughout the experiment.

A lateral fluid percussion injury model was used in the present study. The procedures for brain injury have been described in detail elsewhere (McIntosh et al., 1989; Yuan et al., 1991a). Following a craniotomy, both femoral arteries were cannulated with polyethylene (PE-50) catheters to monitor mean arterial blood pressure (MAP), induce hemorrhage, and sample blood. Both femoral veins were cannulated with PE-50 catheters to infuse anesthetics and resuscitation fluid (via central venous line). Blood temperature was monitored with a microprobe inserted through the brachial artery and positioned in the axillary artery, and the temperature was maintained at 37.2 ± 0.2°C with a heating pad. A total of 1.6 ml of buffered heparinized solution (30 ml of normal saline, 1 ml of 8.4% sodium bicarbonate, 5 ml of distilled water and 4,000 U of heparin sodium) was used to flush the catheters throughout the surgery and the entire experiment.

After completing the instrumentation, 30 min were allowed for hemodynamic stabilization. Then the animals were rotatively assigned to one of four groups: hemorrhagic shock alone (group H, $n = 7$); hemorrhagic shock combined with brain trauma (group TH, $n = 7$); hemorrhagic shock treated with lactated Ringer's solution (group HR, $n = 8$); or hemorrhagic shock combined with brain trauma treated with lactated Ringer's solution (group THR, $n = 8$).

In group H, at 10 min before the initiation of hemorrhage, baseline hemodynamic recordings and blood sampling were performed. At 0.5 min before the hemorrhage, the head was connected to the trauma device for 30 sec (sham injury); and at 0 min, hemorrhage was initiated. Hemorrhagic shock was induced by withdrawing blood (13.5 ml/kg body weight) at a constant rate over 10 min from an arterial cannula using a peristaltic pump. This amount of blood is about 23% of total blood volume of rats (Altmann and Dittmer, 1974). MAP was recorded at 10, 25, 50, and 70 min, and blood samples were collected at 10, 25, and 70 min. At the end of the experiment, humane euthanasia was performed with intravenous administration of 1 ml of 5% sodium pentobarbital.

Group TH was treated exactly as group H except they were subjected to fluid percussion brain injury at 0.5 min before the hemorrhage. The impact level was set at 2.9 atm and the impact duration was maintained at 25 msec.

In groups HR and THR, animals were subjected to the same hemorrhage and the hemorrhage combined with brain trauma as in groups H and TH, respectively. The other experimental procedures were also retained as in groups H and TH. In addition, beginning at the end of the hemorrhage, the animals were resuscitated with a lactated Ringer's solution, which was infused at a constant rate using a peristaltic pump via the central venous line over 10 min. The volume of lactated Ringer's solution given was three times the volume of shed blood.

Variables Measured

An arterial blood sample of 0.7 ml was collected at each of the four sampling times (−10, 10, 25, and 70 min). The first 0.3 ml of blood sample was used to measure arterial blood gases and pH (Instrumentation Laboratory, Lexington, Massachusetts) and blood glucose (glucometer, Model 5550, Miles Laboratories Inc., Elkhart, Indiana). The remaining 0.4 ml of blood was immediately collected in an ice-cooled plastic tube containing 0.8 ml of 8% perchloric acid. These blood samples were centrifuged at 3,000 rpm for 10 min at 4°C and stored at −70°C until assayed for lactate and pyruvate using the lactic dehydrogenase method.

Statistical Analysis

All data are expressed as means ± SEM. The four groups were compared at baseline with a one-way analysis of variance (ANOVA) model. If no significant differences were found in the variables measured, then a three-way analysis of variance was performed to determine the brain trauma, resuscitation, and time effects. Whenever the F statistic was significant, multiple comparisons were performed using the Newman-Keuls test to locate which group means differ. A repeated one-way ANOVA was also performed in each group on all varialbes to determine the overall time effect within a group. Whenever the F statistic was significant, Dunnett's t test was used to compare the three time points to the baseline values within each group. A p value of 0.05 or less was considered significant for all tests.

RESULTS

No significant differences were found in MAP at the end of 10 min hemorrhage among the four groups. Compared with group H, group TH had significantly lower MAP at 50 and 70 min, and group HR had significantly higher MAP at 25, 50, and 70 min ($p < 0.05$) (Fig. 1). Group THR showed no significant difference in MAP compared with group H except for a temporary rise at 25 min ($p \leq 0.05$) (Fig. 1).

Blood Gas and pH Changes

There were no significant differences in blood pH, HCO_3, BE_b, PO_2, and PCO_2 at the baseline among the four groups. Group H showed no significant changes in pH, HCO_3, or BE_b. After hemorrhage, PO_2 was

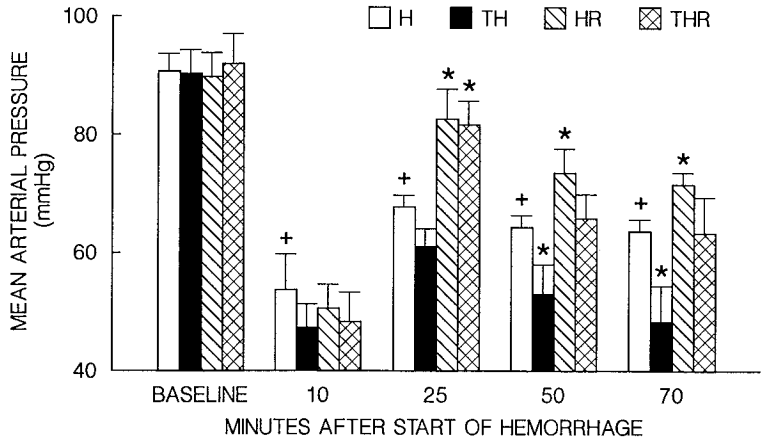

FIG. 1. The effect of brain trauma, fluid resuscitation, or their combination on MAP response to hemorrhage. Group TH had significantly lower and group HR had significantly higher MAP than group H after the hemorrhage or resuscitation. Group THR showed no significant difference with group H except for a temporary rise at T 25. Bars indicate standard error of the mean. +, $p \leq 0.05$ (vs baseline in group H); *, $p \leq 0.05$ (vs group H). Group H: hemorrhage alone; group TH: hemorrhage following brain trauma; group HR: hemorrhage treated with lactated Ringer's solution; group THR: hemorrhage following brain trauma treated with lactated Ringer's solution.

significantly elevated and PCO_2 was significantly decreased. Compared with group H, group TH had significantly lower pH and BE_b after the hemorrhage. At 70 min, the values of pH and BE_b for groups TH versus H were 7.26 ± 0.01 versus 7.31 ± 0.01 and −10.2 ± 1.0 versus −7.8 ± 1.2, respectively. Fluid replacement increased blood pH and BE_b. At 70 min, the pH and BE_b values for group HR were significantly higher than those for group H; the BE_b value for group THR was significantly higher than that for group TH. Blood HCO_3 concentration showed a similar trend, but the change did not attain the significance level. There were no signifiant differences in blood gas and pH values between groups THR and H.

Blood Glucose, Lactate, and Pyruvate Level Changes

There were no significant differences in blood glucose (Table 1), lactate, and pyruvate (Fig. 2) levels at the baseline among the four groups. In group H blood glucose level increased significantly (from 140 ± 15 to 212 ± 16 mg/dl) during hemorrhage and then tapered off, a pattern that was similar in the other three groups. No significant differences among the four groups were found in blood glucose levels at each time point.

In group H, blood lactate level increased significantly (from 4.3 ± 0.7 to 14.7 ± 2.2 mg/dl) during the hemorrhage and then remained significantly higher than the baseline throughout the experiment. Brain trauma increased blood lactate level. At 70 min, group TH showed a significantly higher blood lactate level than group H (26.8 ± 2.9 vs 18.5 ± 1.9). However, infusion of lactated Ringer's solution did not increase blood lactate level. No significant differences in blood lactate levels were found between groups H versus HR or THR. In group H blood pyruvate levels were significantly increased after the hemorrhage. Groups HR, TH ($p < 0.05$), and THR ($p < 0.05$) showed higher blood pyruvate levels than group H after hemorrhage or resuscitation. There were significant increases in the ratios of lactate to pyruvate (L/P) after hemorrhage in group H (Table 1). With brain trauma, this increase was remarkably reduced with a significant difference between groups TH and H at 10 min (101 ± 10 vs 140 ± 11). Resuscitation also significantly reduced this elevated ratio. Group HR showed a significantly higher L/P ratio than group H at 10 min (209 ± 26 vs 140 ± 11), but groups HR and H showed no significant differences in this ratio after resuscitation. Group THR showed lower L/P ratios than group H with significance at 25 min (52 ± 4 vs 86 ± 12).

TABLE I. BLOOD GAS, GLUCOSE LEVELS AND RATIO OF BLOOD LACTATE-PYRUVATE LEVELS

			Min After Start of Hemorrhage		
Variable	*Group*	*Baseline*	*10*	*25*	*70*
PO_2 (mmHg)	H	72 ± 3	96 ± 5[a]	90 ± 5	88 ± 5
	TH	75 ± 5	90 ± 5	86 ± 5	87 ± 6
	HR	75 ± 3	114 ± 4[b]	76 ± 3	91 ± 3
	THR	76 ± 2	102 ± 7	75 ± 6	79 ± 6
PCO_2 (mmHg)	H	37 ± 2	37 ± 2	34 ± 2	32 ± 2[a]
	TH	36 ± 3	34 ± 4	35 ± 2	33 ± 2
	HR	36 ± 3	33 ± 1	36 ± 2	33 ± 1
	THR	37 ± 2	36 ± 2	37 ± 1	36 ± 2
Glucose (gm/dl)	H	140 ± 15	212 ± 16[a]	205 ± 13[a]	152 ± 23
	TH	120 ± 23	221 ± 18	170 ± 17	130 ± 17
	HR	128 ± 15	206 ± 23	157 ± 18	128 ± 18
	THR	154 ± 15	247 ± 22	186 ± 18	152 ± 12
Lactate/pyruvate	H	48 ± 6	140 ± 11[a]	86 ± 12	106 ± 25
	TH	43 ± 4	101 ± 10[b]	80 ± 13	102 ± 16
	HR	41 ± 4	209 ± 26[b]	65 ± 6	82 ± 8
	THR	34 ± 4	114 ± 7	52 ± 4[b]	69 ± 8

[a] $p \leq 0.05$ (vs baseline in group H)
[b] $p \leq 0.05$ (vs group H).
For notations see Figure 1.

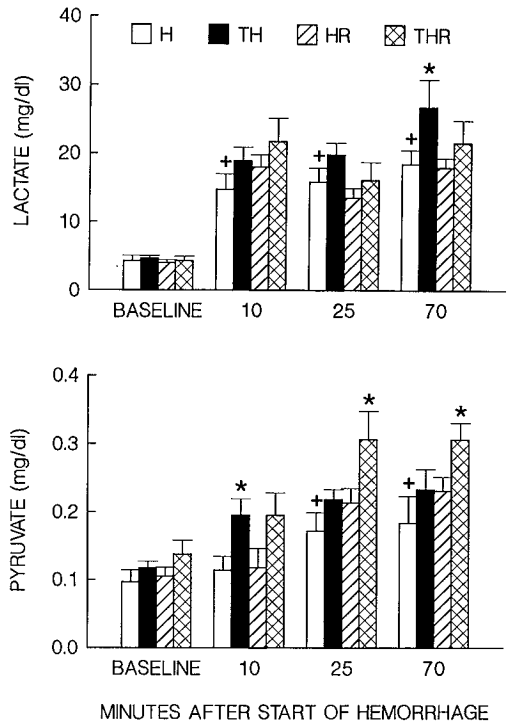

FIG. 2. The effect of brain trauma, fluid resuscitation, or their combination on the responses of blood lactate and pyruvate to hemorrhage. Group H showed a significant increase in blood lactate level after the hemorrhage. Group TH had greater elevations in blood lactate levels over group H. There were no significant differences in blood lactate levels between groups H versus HR or THR. Groups TH and THR showed greater elevations in blood pyruvate levels over group H. Bars indicate standard error of the mean. +, $p \leq 0.05$ (vs baseline in group H); *, $p \leq 0.05$ (vs group H). Group H: hemorrhage alone; group TH: hemorrhage following brain trauma; group HR: hemorrhage treated with lactated Ringer's solution; group THR: hemorrhage following brain trauma treated with lactated Ringer's solution.

DISCUSSION

Our data showed that moderate hemorrhage alone did not cause a marked acid-base disturbance, but the combination of moderate hemorrhage and brain trauma precipitated acidosis. This acidosis was considered to be metabolic because PCO_2 did not change with the addition of brain trauma, but HCO_3 decreased and blood base excess was significantly lower.

Our study also showed that brain trauma aggravated blood lactate accumulation after hemorrhage. Actually, a significant increase in arterial lactate level has been reported in both patients and experimental animals subjected solely to traumatic brain injury without hemorrhage and hypotension (King et al., 1974; Inao et al., 1988). In one study arterial lactate was found to be markedly elevated as early as 15 min following brain trauma (Inao et al., 1988).

Brain trauma-induced blood lactate accumulation may be attributed to several reasons. It has been reported that catecholamines increase blood lactate as much as 350% (Hakanson et al., 1984; Liddell et al., 1979). Within seconds of fluid-percussion brain trauma in the cat, circulating epinephrine rises almost 500-fold and norepinephrine increases nearly 100-fold (Rosner et al., 1984). Although we did not measure catecholamines in the present study, our previous study using the same rat model indicates that the catecholamine responses to hemorrhage are significantly enhanced in the presence of brain trauma (Yuan et al., 1991b). This enhancement may be the major reason for the higher lactate response to hemorrhage in animals with traumatized brains.

The brain may become a substantial source of lactate production after cerebral trauma. One study showed that brain lactate production increased after brain trauma, as evidenced by a negative cerebral arterial-venous lactate difference, which reached the greatest value at 2 h after injury (Inao et al., 1988). Experimental

evidence indicates that trauma-induced cerebral tissue acidosis is due not only to disruption of the brain's oxygen supply, but also to a trauma-induced derangement of cerebral metabolism (McIntosh et al., 1987; Gade et al., 1990). Fluid percussion brain injury in cats leads to a reduction in cerebral tissue pH and a two- to three-fold increase in tissue lactate concentrations when cerebral blood flow is normal (Yang et al., 1985). Evidence exists that mechanical trauma may damage mitochondria, thereby causing a decreased uptake of pyruvate by the mitochondria and resulting in the accumulation of lactate in the cytosol (Duckrow et al., 1981).

Our two resuscitation groups showed no increase in arterial lactate level despite the large amount of lactate infused during the resuscitation. Furthermore, the L/P ratios were reduced in both resuscitated groups as compared with nontreatment groups, indicating that fluid replacement might have relieved tissue hypoxia and increased the conversion of lactate to pyruvate. This therapeutic effect was also reflected in the improved blood gas and pH values in the treatment groups. Group HR showed a significantly higher pH and BE_b than group H. Group THR showed no significant differences in pH, HCO_3, and BE_b compared with group H. However, when animals were not treated with fluid after the combined insults (group TH), the values of pH and BE_b were significantly lower than those in group H. These results indicate that brain trauma-induced lactic acidosis in hemorrhaged animals can be attenuated by an infusion of lactated Ringer's solution.

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DISCLAIMER

The opinions and assertions contained herein are the private views of the authors and are not to be construed as official nor do they reflect the views of the Department of the Army or the Department of Defense (AR 360-5).

The experimental studies of the author described in this report were reviewed and approved by the Institutional Review Committee/Animal Care and Use Committee at Letterman Army Institute of Research. The manuscript was peer reviewed for compliance prior to submission for publication. In conducting the research described here, the author adhered to the *Guide for the Care and Use of Laboratory Animals*, DHEW Publication (NIH) 85-23.

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